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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/685,343	10/11/2000	Pierre Charneau	03495.0197	4371

22852 7590 08/28/2003

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	23

DATE MAILED: 08/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/685,343	CHARNEAU ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-20,22,23,25-28,30-32,42 and 44-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,14-20,22,23,25-28,30-32,42,44-48 and 50-52* is/are rejected.

7)☒ Claim(s) *13 and 49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,9,1121* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/16/03 has been entered.

2. This Action is in response to the communication filed on 6/16/03, as Paper No.22. The amendment has been entered. New claims 44-52 have been added. Claims 11-20, 22, 23, 25-28, 30-32 and 44-42 are currently pending in the application and are examined herein.

3. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim Objections

4. Claims 11-20, 22, 23, 25-28, 30-32, 48 and 49 are objected to because of the following informalities: the claims depended on later numbered claims. For instance, claims 11-20 depend on claim 44, claims 22, 23, and 25-28 depend on claim 45, claims 30-32 depend on claim 46, claim 48 depends on claim 50, and claim 49 depends on objected claim 13 and is therefore also objected to. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 45, 25 and 26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The instant claims are drawn to a process for inserting a heterologous nucleic acid of interest into a nucleus of a target cell, **in vitro** (see claim 45); wherein the heterologous nucleic acid encodes a protein (see claim 25); wherein the protein is a therapeutic protein (see claim 26). Therefore, the claims encompass a process for delivering a heterologous nucleic acid encoding a therapeutic protein to a cell **in vitro**. The only contemplated purpose of delivering a nucleic acid

encoding therapeutic protein to a cell is for therapeutic purposes (i.e. to treat or prevent a disease or disorder). Therefore, the claims encompass a process for delivering a nucleic acid encoding a therapeutic protein for the treatment of a disease or disorder. However, the process is specifically limited to a process for delivering a heterologous nucleic acid to a cell **in vitro** (i.e., the process is carried out in vitro on a cell that is in vitro). The specification does not contemplate any particular use for this **in vitro** process wherein the encoded protein is a therapeutic protein. Therefore, one of skill in the art would not know how to use the claimed process as there is no readily apparent disease or disorder that can be treated by delivering a nucleic acid encoding a therapeutic protein to a cell **in vitro**. In order for one of skill in the art to be able to make/use the claimed invention, it would have to be well known in the art that diseases could be treated by delivering nucleic acids encoding therapeutic proteins to cells in vitro. There is no indication in the art of record at the time of filing that a process for delivering a nucleic acid encoding a therapeutic protein to a cell in vitro could result in the treatment of a disease. Therefore, additional experimentation would have to be performed in order for one of skill in the art to be able to use the invention as claimed. The amount of additional experimentation required is deemed to be undue, considering there are no examples in the art indicating the delivering a nucleic acid encoding a therapeutic protein to a cell in vitro can treat disease.

7. Claims 50-52 and 48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

8. The instant claims are drawn to an isolated/purified nucleic acid comprising retroviral Ψ packaging sequences, cis-acting nuclei acid sequences for reverse transcription and virus integration, (optionally) a cis acting RRE, at least one cPPT sequence and at least on CTS sequence **wherein any other sequences of *pol* is absent**, and a heterologous nucleic acid sequence of interest; as well as methods of using said nucleic acid for delivering the nucleic acid sequence to the nucleus of a target cell for expressing a gene of interest encoded by the heterologous nucleic acid sequence.

9. The limitation that is at least one cPPT sequence and at least on CTS sequence **wherein any other sequences of *pol* is absent** is new matter because the specification does not explicitly indicate that the nucleic acid comprises only cPPT and CTS sequences of *pol*, but no other pol sequences. Applicants argue in the amendment filed 6/16/03 that the specification has implicit basis for this limitation for several reasons (see pages 11-14 of paper filed 6/16/03) including the deposit declaration, the reference teaching the construction of the base plasmid pHR' (Naldini), and other publications relating to *pol* sequences and vectors. However, these arguments are not persuasive because, not only does the specification not have basis for the indicated sequences without any other *pol* sequence, the specification indicates that the sequence does have other *pol* sequences. Specifically, the specification indicates,

> "A 178 bp fragment of pLAI3 (4793 to 4971), **encompassing cPPT and CTS,** was amplified by PCR. NarI restriction sites were added in 5' of the primers with the aim of inserting this fragment into the unique ClaI site of HR GFP..." (Emphasis added, See p. 31, lines 9-12).

This statement clearly indicates that a 178 bp PCR fragment comprising both the cPPT sequence and the CTS sequence, as well as the intervening *pol* sequence is present in the vector. Therefore, the specification does not provided basis for a nucleic acid having at least one cPPT sequence and at least on CTS sequence **wherein any other sequences of *pol* is absent.**

It is noted that the claims can be amended to reflect that the nucleic acid comprises the 178bp fragment comprising the cPPT and CTS sequence and no other *pol* sequence.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 11, 12, 14-20, 22, 23, 25, 27, 28, 30-32, and 44-47 are rejected under 35 U.S.C. 102(b) as being anticipated by Zufferey et al. (Nature Biotech. 1997 cited in IDS filed as Paper No. 4).

Zufferey teaches an isolated/purified nucleic acid comprising retroviral Ψ packaging sequences, cis-acting nuclei acid sequences for reverse transcription and virus integration, a cis acting RRE, a pol gene which comprises at least one cPPT sequence and at least on CTS sequence, and a heterologous nucleic acid sequence of interest; as well as methods of using said

nucleic acid for delivering the nucleic acid sequence to the nucleus of a target cell for expressing a gene of interest encoded by the heterologous nucleic acid sequence.

Specifically, Zufferey teaches, an HIV-1 based vector "in which the expression cassette for the transgene is flanked by the HIV-1-derived cis-acting sequences necessary for packaging, reverse transcription and integration" (see p. 871, last paragraph). Zufferey indicates that the transgene of the vector can be a reporter gene, such as Luciferase or lacZ (e.g., see p. 873, Table 1, Table 2). Zufferey teaches methods of using the vector to deliver the transgene into cells where it is expressed (indicating delivery to the nucleus) as well as assays which encompass isolating the reporter gene and assaying for its presence/activity (e.g., see Tables 1, 2). It is noted, as set forth in a previous Office Action, that HIV-1 based vectors were known to infect non-dividing cells as well as HeLa cells and hematopoietic stem cells.

Regarding claims 44-46, it is noted that the claims are drawn to nucleic acid sequences comprising retroviral sequences consisting of at least one cPPT sequence and at least one CTS sequence. This claim encompasses any nucleic acid sequence comprising a retroviral sequence having at least one cPPT and CTS sequence. The vector taught by Zufferey includes a pol sequence that includes a cPPT and CTS sequence.

Regarding claim 47, drawn to a nucleic acid comprising the *ClaI* insert and *Eco*RI/*Bam*HI insert of pTRIPΔU3EF1αGFP, it is noted that the claim encompasses any nucleic acid encoding these inserts. Based on the disclosure in the specification it appears that the inserts comprise the CMV promoter sequence, and the cPPT and CTS sequences. Zufferey teaches a HIV-1 based vector comprising the CMV promoter and pol sequence that comprises cPPT and CTS sequences (e.g., see Fig. 3, p. 873).

It is noted that limiting the claims to the vector that is pTRIPΔU3EF1αGFP and methods of using this vector for delivering a nucleic acid of interest to cells in vitro and expressing the transgene in cells in vitro would be free of the prior art.

Response to Arguments

The previous rejections of claims 41 and 43 under 35 USC 102(b) and claim 35 under 35 USC 103 are now moot as these claims have been cancelled.

The previous rejections of claims 1 and 8-32 under 35 USC 112 have been withdrawn in view of the amendment/new claims/cancellation of claims.

Allowable Subject Matter

12. Claims 13 and 49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell

DAVE T. NGUYEN
PRIMARY EXAMINER